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A FIRST AND GENERAL ROUTE TO NAPHTHYLISOQUINOLINE ALKALOIDS: THE TOTAL SYNTHESIS OF O-METHYL-TETRADEHYDRO-TRIPHYOPHYLLINE[1,2]

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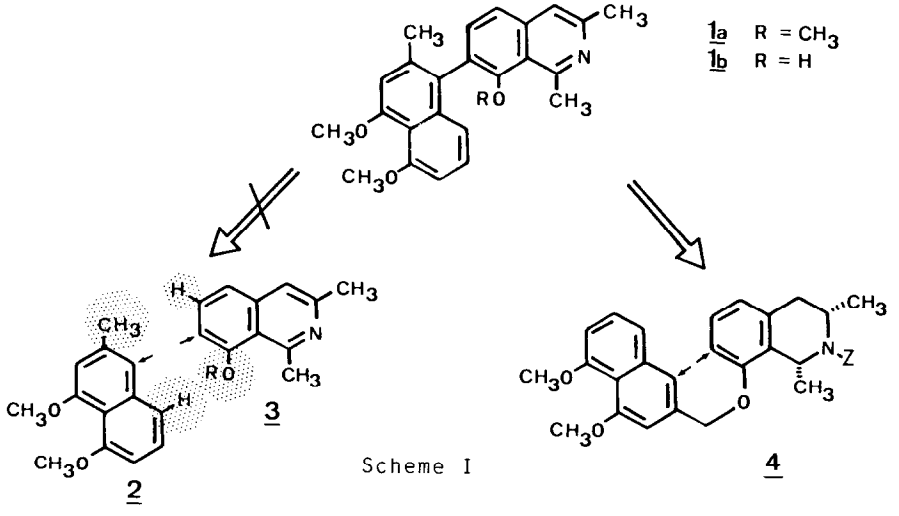
Summary: The first total synthesis of a naphthylisoquinoline alkaloid is described. The required ortho selective mixed coupling of the alkaloid moieties **2** and **6** is achieved intramolecularly by the assistance of a reversibly thrown benzylether type auxiliary bridge.

O-Methyl-tetradehydro-triphyophylline (**1a**)[3] belongs to a group of structurally and physiologically interesting compounds isolated from tropical lianas of the genera Triphyophyllum[3-5] and Ancistrocladus[6], formally to be classified into the vast group of isoquinoline alkaloids. Model reactions in vitro[7,8], however, suggest that the unique substitution pattern of these alkaloids may arise by a hitherto unprecedented isoquinoline biogenesis from acetate, via ß-polyketones, rather than by the conventional "Mannich-type" pathway from aromatic amino acids[9].

We now wish to describe a first and general route to synthetic naphthylisoquinoline alkaloids, important not only for modelling the proposed biogenetic scheme, but also for gaining the alkaloids and their analogues for biological tests, as well as for a verification of published structures.

Based on our biomimetic cyclization reactions of polyketones like **5** – optionally leading to the naphthalene **2** and the isoquinoline **6** [7,8] - the completion of our first synthesis now still demands the regioselective coupling of these two different, sterically crowded aromatic systems, direct methods[10] like the classical Ullmann reaction giving most unsatisfying results[11].



Scheme I

Consequently, in the attempt to learn - here as well - from nature, where enzymes may enforce the desired mixed coupling by holding the two arenes at a suitable distance and angle, we have thrown a chemical auxiliary bridge from the naphthalene **2** to the isoquinoline **3**, considering a benzylether type compound like **4** a promising precursor to **1** rather than the two isolated moieties **2** and **3** (see scheme I).

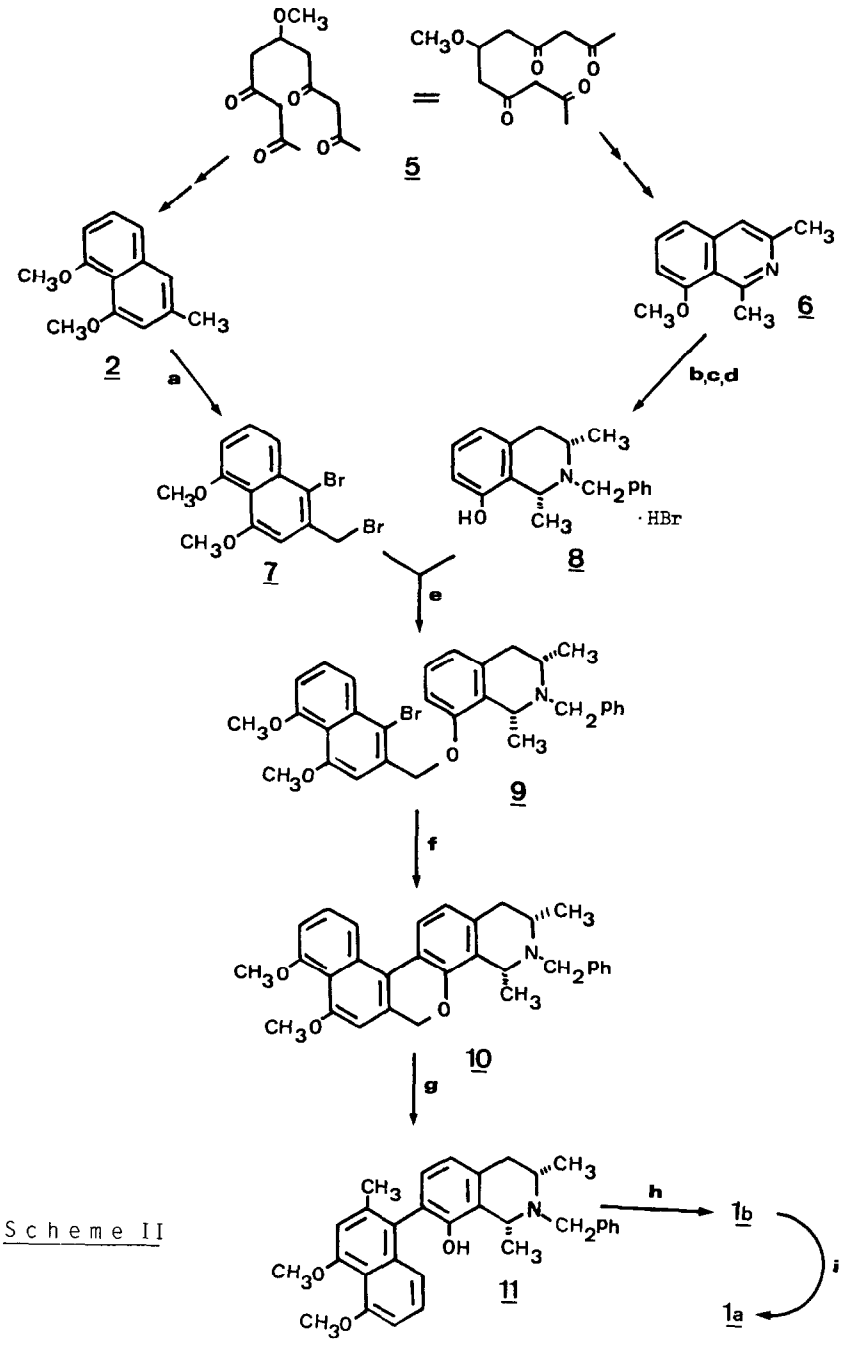
The translation of this concept into reality shows that this type of a bridge fully comes up to our expectations. Thus, isoquinoline **6** is reduced either with Zn/HCl (reflux, 24 hrs) to a mixture of diastereomeric tetrahydro-isoquinolines (cis/trans ratio = 59/41; separation on silicagel/ether), or by cis-selective catalytic hydrogenation (PtO_2) of **6** HBr. N-Benzylation and subsequent O-demethylation delivers the desired tetrahydro-isoquinoline **8** as its hydrobromide[12], whereas double functionalization of **2** to **7**[12] is carried out in one step only, using NBS with nearly equimolar amounts of azo-bis-isobutyronitrile (AIBN) as initiator, in refluxing cyclohexane.

Pre-fixation of the two moieties to **9**[12] smoothly occurs by quantitative phase transfer catalysed O-selective alkylation of **8** with **7**. The desired aryl aryl coupling, now intramolecularly performed[13] by photolysis of **9** leads to the six-membered ring ether **10**[12], along with hydro-dehalogenation (15 %) and recovery of starting material **9**.

The benzylether type auxil iary C-O bond - in **9** definitively the Achilles heel towards reductive and ether cleaving reagents[14,15] - proves to be astonishingly resistant in the flattened[16] cyclic ether **10**[17]. The desired reductive ring opening can - nonetheless - very smoothly be brought about with dilithio biphenyl[18] - a potent reagent[19] only rarely applied in organic synthesis - directly creating the o-hydroxy-o'-methyl biphenyl subunit, structural feature of naphthylisoquinoline alkaloids. The resulting tetrahydro isoquinoline **11**[12], which occurs as atropisomers[20], can be dehydrogenated catalytically, under simultaneous debenzylation to the known naphthylisoquinoline **1b** mp 272 °C (lit.[1] mp 272 °C), itself dehydrogenation product of native tetrahydro isoquinoline alkaloids from Triphyophyllum peltatum, thus confirming the constitution of these natural products.

O-Methylation leads to the title compound O-methyl-tetradehydro-triphyophylline (**1a**), mp 166 °C (lit.[1] mp 116 °C), described as a natural product in this racemic form (lit.[1] $\alpha_D = 0^0$).

This very first synthesis of a naphthylisoquinoline alkaloid demonstrates the efficiency of our concept of a benzylether bridge assisted aryl aryl coupling, and thereby opens up the variable methodical basis for the rational synthesis of further, related alkaloids, this work is in progress.



Scheme II

(a) NBS, AIBN, C_6H_{12}, reflux; 63 %. (b) H_2, PtO_2, CH_3OH, $HClO_4$; 92 %. (c) $PhCH_2Br$, n-C_3H_7OH, K_2CO_3; 85 %. (d) 48 % aqueous HBr, reflux; 94 %. (e) $PhCH_2N^+(n\text{-}C_4H_9)_3$, CH_2Cl_2, 1n NaOH; 93 %. (f) 254 nm, C_6H_{12}, NEt_3; 15 %. (g) Li, $(C_6H_5)_2$, THF, -100° C; 78 %. (h) 10 % Pd/C, trans decalin, reflux; 69 %. (i) $PhCH_2N^+(n\text{-}C_4H_9)_3$, $(CH_3)_2SO_4$, CH_2Cl_2, 1n NaOH, 86 %.

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References and notes:

1. Dedicated to Professor Sir Derek H.R. Barton on the occasion of his 65th birthday.
2. This work was presented in part at the 29th IUPAC congress in Köln, FRG, June 6, 1983.
3. M. Lavault and J. Bruneton; C. R. Hebd. Acad. Sci., Ser. B 1978, 287, 129.
4. M. Lavault, M.T. Kouhon and J. Bruneton; Ibid. 1977, 285, 167.
5. J. Bruneton, A. Bouquet, A. Fournet and A. Cavé; Phytochemistry 1976, 15, 817.
6. For a review, see: T.R. Govindachari and P.C. Parthasarathy; Heterocycles 1977, 7, 661.
7. G. Bringmann; Angew. Chem., Int. Ed. Engl. 1982, 21, 200.
8. G. Bringmann; Tetrahedron Lett. 1982, 23, 2009.
9. D.R. Dalton "The Alkaloids"; Marcel Dekker Inc.: New York 1979.
10. For a review, see: M. Sainsbury; Tetrahedron 1980, 36, 3327.
11. Thus, reaction of the two moieties in their brominated forms with activated copper bronze at 250 ^{o}C leads to mixed coupled products in traces (<1 %), only.
12. Satisfactory elemental analyses, as well as IR (KBr, cm^{-1}), ^{1}H-NMR (300 MHz, δ/ppm), UV ($CHCl_3$, λ_{max}, (log ε)), and mass spectra were obtained for all new compounds, representative data follow: **7** : mp 144 ^{o}C; IR 1610, 1595, 1570, 1270; NMR 3.97 (s, 3 H), 3.99 (s, 3 H), 4.80 (s, 2 H). **8**: mp 185-187 ^{o}C; IR 3500, 2700-2600, 1600; NMR (CD_3OD) 1.48 (d, J = 7.1 Hz, 3 H), 1.68 (d, J = 6.7 Hz, 3 H), 2.55 (m, 1 H), 3.0-3.15 (m, 2 H), 4.27 (d, J = 13.2 Hz, 1 H), 4.57 (d, J = 13.2 Hz, 1 H), 5.04 (q, J = 7.1 Hz, 1 H). **9** : mp 106-107 ^{o}C; IR 1590, 1570, 1260; NMR 5.24 (d, J = 13.2 Hz, 1 H), 5.30 (d, J = 13.2 Hz, 1 H). **10**: mp 157-159 ^{o}C; IR 1590, 1580, 1260; NMR 4.91 (d, J = 13.0 Hz, 1 H), 5.01 (d, J = 13.0 Hz, 1 H); UV 331 (4.2), 345 (4.3), 361 (4.2), 367 (3.0) nm. **11**: mp 176/244 ^{o}C, 2 separated atropisomers, see footnote 20.; IR 3450, 1610, 1590, 1570; NMR 2.21 (s, 3 H), 4.68 (s, 1 H)/2.19 (s, 3 H), 4.72 (s, 1 H); UV 305 (4.0), 319 (4.0), 334 (3.9) nm.
13. Analogous intermolecular photolysis leads to quantitative hydro-dehalogenation (95 %) with no aryl coupling observed, not to mention the desired o-orientation.
14. For a recent review, see: M.V. Bhatt and S.U. Kulkarni; Synthesis 1983, 249.
15. **9** is easily cleaved into its molecular moieties by H_2/Pd-C, BBr_3, trifluoracetic acid, etc.
16. This planarization - manifest from an observed bathochrome shift (compared with compd. **11** , see footnote 12) from partial π-overlap - leads to macroscopically lacking (NMR, t.l.c.) atropisomerism.
17. Thus, prolonged attack of H_2/Pd-C leads to aromatic hydrogenation, whereas BBr_3 preferably cleaves the methylethers.
18. J.J. Eisch; J. Org. Chem. 1963, 28, 707.
19. G. Bringmann and J.R. Jansen; unpublished results.
20. The separation of these atropisomers, which is not necessary here, can be brought about by fractioned crystallization (ether, methanol) and H.P.L.C. (SiO_2, $CHCl_3$/Ether = 2/1).

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